Manganese
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Bouchard, M., LaForest, F., Vandelac, L. et al. 2007. Hair Manganese and Hyperactive Behaviors: Pilot Study of School-Age Children Exposed through Tap Water. Environmental Health Perspectives. 115(1): 122-127.

Bouchard et al. (2007) studied 46 Canadian children and the relationship between exposure to manganese in drinking water and neurobehavioral effects. The children ranged in age from 6 to 15 years, with a median of 11 years. Water was received from one of two wells: the first well (W1) had a mean manganese concentration of 610 µg/L and the second (W2) had a mean concentration of 160 µg/L. Twenty-eight children (61%) received their drinking water from W1 and 18 (39%) from W2. Manganese hair levels were measured, with an average concentration of 5.1 ± 4.3 µg/g. Girls had significantly higher levels of manganese in hair than boys (mean of 6.3 ± 4.4 µg/g vs. 4.0 ± 4.0 µg/g, t-test, $p < 0.01$) and children who received water from W1 had higher levels of manganese in hair than those who received water from W2 (mean of 6.2 ± 4.7 µg/g vs. 3.3 ± 3.0 µg/g, t-test, $p = 0.025$).

Behavioral effects were measured using the Revised Conners' Rating Scale for parents (CPRS-R) and for teachers (CTRS-R), with T-scores on the following tests: Oppositional, Hyperactivity, Cognitive Problems/Inattention, and Attention Deficit/Hyperactive Disorder (ADHD) Index. Manganese levels in hair were significantly and positively associated with CTRS-R T scores on the Oppositional test ($p = 0.020$) and Hyperactivity test ($p = 0.002$) after adjusting for age, sex, and income. All children who had T scores of ≥ 65 on the Oppositional and Hyperactivity tests of CTRS-R had manganese levels in hair > 3.0 µg/g. The T scores for CTRS-R Cognitive Problems/Inattention ($p = 0.085$) and ADHD ($p = 0.062$) tests approached significance, while there was no significant relationship between levels of manganese in hair and the T scores on any of the CPRS-R tests.

The authors concluded that children living in homes using water from the well with higher manganese concentrations had higher manganese levels in hair, which was associated with increased hyperactive and oppositional behavior in the classroom. The authors did not identify a concentration level of manganese in water that was associated with the increase in behavioral effects. The authors also concluded that follow-up studies were needed to determine whether these behaviors continue after manganese concentrations are reduced in drinking water.

Bouchard, M.F., Sauve, S., Barbeau, B. 2011. Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water. Environmental Health Perspectives. 119(1): 138-143.

In Bouchard et al. (2011), the relationship between manganese exposure in drinking water and intellectual impairment in children was investigated. In addition, the associations between hair manganese concentration and manganese exposures from drinking water and from the diet were examined. A total of 362 children, ages 6-13 years old were studied, and data included analysis of manganese in the children's hair and tap water from the children's homes. The median level of manganese in tap water in the children's homes was 34 µg/L (range 1-2,700 µg/L). The levels of manganese in tap water were divided into five quintiles for the analysis of the data (median and ranges of manganese concentrations presented): 1st quintile (lowest): 1 µg/L (0-2 µg/L), 2nd quintile: 6 µg/L (3-19 µg/L), 3rd quintile: 34 µg/L (20-66 µg/L), 4th quintile: 112 µg/L (67-153 µg/L), and 5th quintile (highest): 216 µg/L (154 – 2,700 µg/L). A semi-quantitative food frequency questionnaire was administered to the parents and the children to assess manganese consumption from the diet and water. Manganese levels in children's hair were measured, with levels ranging from 0.1 – 21 µg/g. The Wechsler Abbreviated Scale of Intelligence was used to assess general cognitive abilities, measuring a Verbal IQ score, a Performance IQ score, and a Full Scale IQ score.

Children's manganese hair levels were significantly associated with manganese water intake ($p < 0.001$) but not with the estimated manganese dietary intake ($p = 0.76$). No significant association was noted between estimated dietary manganese intake and IQ scores, either adjusted or unadjusted (results not presented). However, manganese in tap water in the children's homes, manganese in hair, and estimated manganese intake from water were significantly associated with lower Full IQ scores in two adjusted models. The associations between manganese levels and lower Full Scale IQ scores are as follows (changes in IQ scores for a 10-fold increase in indicators of manganese exposure β): Manganese in water - Model A: $\beta = -1.9$ (95th CI, -3.1 to -0.7) and Model B: $\beta = -2.4$ (95th CI, -3.9 to -0.9); Manganese in hair – Model A : $\beta = -3.7$ (95th CI, -6.5 to -0.8) and Model B: : $\beta = -3.3$ (95th CI, -6.1 to -0.5); Estimated Manganese intake from water – Model A: $\beta = -1.2$ (95th CI, -2.3 to -0.1) and Model B: $\beta = -1.2$ (95th CI, -2.3 to -0.1). Manganese in tap water was more strongly associated with Performance IQ than Verbal IQ, as shown in the following associations: Performance IQ – Model A: $\beta = -2.3$ (95th CI, -3.7 to -0.8) and Model B: $\beta = -3.1$ (95th CI, -4.9 to -1.3); Verbal IQ - Model A: $\beta = -1.5$ (95th CI, -2.6 to -0.3) and Model B: $\beta = -1.2$ (95th CI, -2.7 to 0.3).

The authors concluded that children exposed to higher manganese concentrations in tap water had lower IQ scores. An increase in manganese in tap water by 10-fold was associated with a decrease of 2.4 IQ points (95th CI, -3.9 to -0.9. $p<0.01$), after adjusting for maternal intelligence, family income, and other potential confounders. A 6.2 Full Scale IQ point difference was found between the children exposed to water at 1 µg/L and 216 µg/L (median of the lowest and highest quintiles, respectively, for concentrations of manganese in tap water). Manganese in tap water was more strongly associated with Performance IQ than Verbal IQ.

Boyes, W.K. Essentiality, Toxicity, and Uncertainty in the Risk Assessment of Manganese. 2010. Journal of Toxicology and Environmental Health, Part A. 73: 159-165.

Boyes (2010) summarized the EPA's risk assessments on manganese. In 1993, the EPA published a Reference Concentration (RfC) of 0.05 $\mu g/m^3$ for inhaled manganese, based on neurobehavioral and motor movement impairments in workers exposed to manganese dioxide in a Belgian battery factory (Roels et al., 1987, 1992). The exposure concentration in the Roels et al. study was considered to be a LOAEL and was divided by standard uncertainty factors for noncancer health effects. The nutritional essentiality of manganese was not factored into the RfC.

In 1996, the EPA established a Reference Dose (RfD) for oral exposure to manganese of 0.14 mg/kg/day, based on the essentiality of manganese. The National Research Council had established a range of manganese of 2-5 mg/day as an estimated safe and adequate daily dietary intake. The range included a margin of safety and consumption of 10 mg/day was considered safe for occasional intake. The EPA assumed the upper level of the range of dietary essentiality of 10 mg/day as a starting value and converted it to mg/kg/day by dividing it by 70 kg (the standard weight of an adult male), resulting in an RfD of 0.14 mg/kg/day[1].

These risk assessments did not characterize manganese body burden or mass balance. However, as a result of discussions between the EPA and the Ethyl Corporation related to a petition for registration of the fuel additive containing manganese, methylcyclopentadienyl manganese tricarbonyl (MMT), culminating in the EPA's Fuel and Fuel Additives Test Rule, a large dataset of manganese pharmacokinetics has been developed, allowing the development of physiologically based pharmacokinetic (PBPK) models of manganese. These models can assess the impact of inhaled manganese against different dietary loads and make quantitative extrapolations across dose levels and durations of exposure. It remains to be determined as to the extent to which the manganese PBPK models will be used in upcoming risk assessments.

Deveau, M. 2010. A Contribution of Drinking Water to Dietary Requirements of Essential Metals. Journal of Toxicology and Environmental Health. Part A, 73: 235-241.

Deveau (2010) compared the intake of six essential elements (chromium, copper, iron, manganese, selenium, and zinc) from drinking water and the recommended dietary allowance (RDA) or adequate intake (AI) values derived by the Institute of Medicine. This study compared the intake of these elements at guideline levels established by Health Canada, the EPA, and the World Health Organization (WHO), as well as the intake of these elements from drinking water at typical concentrations observed in Canada with the recommended dietary reference intake values.

[1] For exposures via drinking water IRIS recommends application of a 3-fold modifying factor to the RfD (0.014/3 = 0.05 mg/kg/day)

The percent contribution to the dietary reference intake for exposure to manganese through drinking water at typical Canadian levels was: 100% for bottle-fed infants; 3% for ages 7-12 months; 1% for young children, older children, adolescents and adult males; and 2% for adult females. The percent contribution to the daily reference intake if individuals were consuming water containing maximum levels of manganese according to the guideline levels set by Health Canada was: 100% for bottle-fed infants; 7% for 7-12 months; 3% for 1-3 year olds; 2-3% for 4 – 13 year olds, and 3-4 % for adolescents and adults. The author concluded that elements in drinking water at typical levels contribute only slightly to their dietary requirements.

Dorman, D.C. and Wong, B.A. 2005. Neurotoxicity of inhaled manganese: A reanalysis of human exposure arising from showering. Doi:10.1016/j.mehy.2005.08.001.

Dorman and Wong (2005) is a correspondence that discusses the use of their data in Elsner and Spangler (2005).

According to Dorman and Wong (2005), Elsner and Spangler (2005) significantly over-predicted human exposure to manganese in the shower based on a misunderstanding of their data. The misunderstanding resulted from the presumption that a residential showerhead and a vibrating orifice aerosol generator produced similar sized liquid particles and thus the relative amount of manganese inhaled by the human and rat could be directly related to the respective manganese concentrations in the water source. The authors carried out an alternative calculation that showed that the potential for human neurotoxicity from showering was overestimated and that inhalation of manganese during showering does not present a neurological health risk.

Erikson, K.M., Thompson, K., Aschner, J. et al. 2007. Manganese neurotoxicity: A focus on the neonate. Pharmacology and Therapeutics. 113: 369-377.

Erikson et al. (2007) is a review of manganese neurotoxicity, with emphasis on the neonate. Three topics are reviewed: manganese transport into the brain, modes of manganese exposure, and mechanisms of manganese neurotoxicity. Manganese in plasma is bound to carriers such as albumin, citrate, divalent metal transporter 1 and transferrin. When complexed with transferrin, manganese is exclusively present in the trivalent oxidation state. The complex can enter the endothelial cells, where it may be taken up by neurons in the brain. Other potential transporters of manganese are currently under investigation, including a monocarboxylate transporter, organic anion transporter polypeptide, ATP-binding cassette, calcium channels, or ZIP transporter proteins.

The main source of manganese exposure for the general population is the diet, with most daily intakes falling below 5 mg Mn/kg. Another important source of dietary manganese intake is dietary supplements, with many containing manganese at concentrations of 5-20 mg. Water concentrations of manganese are generally low, typically ranging from 1 to 100 µg/L, with most

below 10 µg/L. Human milk is generally low in manganese, however higher concentrations have been observed in infant formula, ranging from 33-300 µg/L. High concentrations have also been reported in soy-based formula, ranging from 200 – 300 µg/L. Manganese concentrations in total parenteral nutrition (TPN) solutions range from 5.6 to 8.9 µg/L.

Mechanisms of neurotoxicity for manganese are currently under investigation. Oxidative stress with the oxidation of dopamine, formation of reactive oxidative species in the mitochondria, and inhibition of high affinity glutamate transporters with subsequent increase in extracellular glutamate are possible mechanisms. Rats exposed to manganese through inhalation during gestation and during post-natal days 1-19 had significantly decreased glutathione and decreased gene expression of metallothionein and glutamine synthetase (two markers of oxidative stress) in the striatum of the brain. These studies appear to indicate that the striatum is a vulnerable brain region in the neonate. Further studies need to be done in this area, including investigating whether manganese exposure during early development increases the risk for developing neurological diseases later in life.

Fordahl, S., Cooney, P., Qui, Y. et al. 2012. Waterborne manganese exposure alters plasma, brain, and liver metabolites accompanied by changes in stereotypic behaviors. Neurotoxicology and Teratology. 34: 27-36.

Fordahl et al. (2012) investigated potential biomarkers for manganese neurotoxicity and changes in behavior in weanling rats indicative of neurotoxicity. Male Sprague-Dawley rats (6/dose) ingested manganese in drinking water at 0 or 100 mg/kg/day for 6 weeks. Behavioral analysis during the 4^{th}, 5^{th}, and 6^{th} week of exposure examined hyperactivity and altered locomotion. Manganese levels in the brain, liver, plasma and analysis of metabolites in these tissues were carried out after the animals were sacrificed during the 7^{th} week of the study.

Significantly higher manganese levels were detected in the brain, liver, and plasma of exposed rats compared to controls ($p<0.05$). Altered metabolites were also detected in these tissues, impacting cholesterol and fatty acid metabolism in the brain (increased oleic and palmitic acids) and liver (increased oleic acid and decreased hydroxybutyric acid), and increased homogentisic acid and chenodeoxycholic acid, and decreased aspartic acid in plasma. Significantly increased locomotion and a significant increase in repetitive turning during the light cycle and a significant decrease in rearing during the dark cycle were noted for the manganese-exposed rats ($p<0.05$). The authors concluded that this study identified several biomarkers that could be used for manganese neurotoxicity and that manganese affects locomotion and disrupts the circadian cycle in rats.

Golub, M.S., Hogrefe, C.E., Germann, S.L. et al. 2005. Neurobehavioral evaluation of rhesus monkey infants fed cow's mild formula, soy formula, or soy formula with added manganese. Neurotoxicology and Teratology. 27: 615-627.

Golub et al. (2005) investigated the neurobehavioral effects from excess manganese in infant soy formula in monkeys. Newborn male Rhesus monkeys (8 per group) were fed a diet of commercial cow's milk-based infant formula, commercial soy formula, or commercial soy formula with added manganese (as chloride) at 1000 µg/L from birth to 4 months of age. Manganese doses were estimated as 18 mg/kg/day for the Control group (cow's milk-based formula); 106 mg/kg/day for the Soy group, and 323 mg/kg/day for the Soy with Manganese group.

A battery of behavioral tests were carried out from birth to 18 months of age as follows: motor development (1-14 weeks), dyadic social interaction (1-5.5 months), automated activity monitoring (4, 8 months), Wisconsin General Test Apparatus tests of object discrimination learning (5-8 months), object discrimination reversal (8-9 months), delayed nonmatch to sample training (9-10.5 months), delayed nonmatch to sample test (10.5 to 11.5 months), position learning and reversal (11.5-12.5 months), post-session temperament score (8-12.5 months), and reward delay (12.5 months); and Cambridge Neuropsychological Test Automated Batteries (CANTAB) tests of fixed interval training (13-16 months), dopamine drug challenge (16 months), continuous performance test (17-18 months), and stereotypy observations (18 months). In addition, iron absorption studies were carried out at 4 and 8 months and cerebrospinal fluid (CSF) catecholamine samples for detection of metabolites were carried out at 4, 10, and 12 months.

No differences were observed among groups on growth, health, developmental milestones, temperament ratings, or stereotypy. In addition, no differences were observed on the tests used to assess learning, memory, or attention (delayed nonmatch to sample, object discrimination, position discrimination and reversal, and continuous performance test). However, the following differences were noted between the groups:

- Poorer participation in all tasks in the Soy group compared to the other groups,
- Greater responsiveness in the Soy plus manganese group in the early sessions of the continuous performance test, which reversed later in the sessions, and
- Slower attainment of the position discrimination task criteria and lack of improvement in the reward delay task in the Soy plus manganese group.

Several endpoints were statistically significantly different between the Control and Soy group and Control and Soy plus manganese group on the following behavioral tests: duration of the daily sleep pattern, the frequency of cling and play behaviors during dyadic interaction, and premature responding during the reward delay test. These results correspond to less play

behavior, more clinging behavior, shorter wake cycles, and shorter periods of daytime activity in the Soy groups compared to the control group. There were no significant differences between the groups in CSF monoamine metabolite concentrations. The authors concluded that components in soy formula, including manganese, could affect brain development, as measured in behavioral tests. The controls were given a milk-based formula rather than a soy formula.

Henn, B.C., Ettinger, A.S., Schwartz, J. et al. 2010. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology. 21(4):433-439.

Henn et al. (2010) is a prospective epidemiological study on 448 children born in Mexico City from 1997 to 2000. Blood samples were obtained from the children at 12 or 24 months of age and analyzed for manganese. Child neurodevelopment was assessed at 6 month intervals between 12 and 36 months of age using the Bayley Scales of Infant Development-II: Mental Development Index and Psychomotor Development Index. Information on factors that could be potential confounders, including sex, umbilical cord blood lead, birth weight, birth length, head circumference at birth, gestational age, hemoglobin and ferritin levels, maternal age at delivery, maternal and paternal education, maternal marital status, maternal blood lead levels at 1 month postpartum, duration of breast feeding in the infant's first year, child nutrition, and maternal IQ, were collected at delivery, 1 month postpartum, and during subsequent study visits.

The mean blood manganese level at 12 months of age was 24.3 µg/L and the median was 23.7 µg/L. These values were 21.1 µg/L and 20.3 µg/L, respectively, at 24 months of age. The results did not differ significantly between boys and girls. Blood lead was positively associated with 24-month manganese levels ($\beta = 0.34$, 95% CI = 0.11 – 0.58), while hemoglobin, ferritin, birth weight, and gestational age were inversely associated with manganese at both 12 and 24 months.

A nonlinear association was observed between 12 month manganese blood levels and the 12-month Mental Development Index ($p = 0.04$). An adjusted multivariable regression blood model was fit with indicator variables for five quintiles of blood manganese levels (Quintile 1= 15.3 – 20.1 µg/L; Quintile 2 = 20.2 – 22.4 µg/L; Quintile 3 = 22.5 – 25.1 µg/L; Quintile 4 = 25.2 – 28.0 µg/L; Quintile 5 = > 28.0 µg/L). Lower 12-month development scores were observed among children with 12-month manganese levels in the lowest and highest quintiles, compared with children in the middle three quintiles. No association was noted between 24-month manganese levels with 24- or 36-month Mental Development Index scores.

The authors explained the inverted U-shaped association between manganese levels at 12 months of age and mental development scores as possibly being due to the effects of manganese on oxidative stress at low and high levels. Manganese is a cofactor for enzymes that protect against oxidative stress; manganese deficiency could increase sensitivity to oxidative cellular injury

while manganese excess could cause oxidative damage since manganese catalyzes oxidative reactions in neurologic tissues.

Kern, C.H., Stanwood, G.D., and Smith, D.R. 2010. Preweaning manganese exposure causes hyperactivity, disinhibition, and spatial learning and memory deficits associated with altered dopamine receptor and transporter levels. Synapse. 64: 363-378.

In Kern et al. (2010), neonatal Sprague-Dawley rats were exposed to oral doses of 0, 25, or 50 mg/kg/day manganese over postnatal day (PND) 1-21. On PND 23, 23 cohorts of rats were tested in the open arena test for spontaneous locomotor activity (n = 15-20 males/group) and the elevated plus maze test for anxiety-related behavior (n = 7/males/group). Animals were sacrificed on PND 24 for measurement of manganese levels in the blood and brain and levels of dopamine D1 and D2 receptor proteins and the dopamine transporter (DAT) in the brain. Another cohort (n = 15-20 males/group) were tested in an 8-arm radial maze for spatial memory and stimulus response learning, using a 6-day maze acclimation period on PND 27-32 followed by a 14-day testing period on PND 33-46. A group of female rats was sacrificed on PND 36 to examine manganese levels in the blood and brain at the same time as the 8-arm radial maze testing.

Preweaning manganese exposure caused a significant increase in distance traveled in the open arena in male rats ($p = 0.01$), with the 25 mg/kg/day and 50 mg/kg/day groups showing approximately a 12% and 20% increase in total distance traveled, respectively, compared to the controls ($p<0.05$). A significant increase in center zone activity in male rats in the open arena was observed in the exposed rats at 50 mg/kg/day compared to the controls, based on the ratio of center/total distance travelled ($p=0.01$). No difference was noted in the elevated plus maze performance; however differences were noted in the all of the learning tests. In the 8-arm radial maze, 100% of the control rats reached the learning criterion over the 14-day testing period, compared to only 83% or 62% of the rats exposed to 25 or 50 mg/kg/day, respectively. The 50 mg/kg/day group differed significantly from the controls and the 25 mg/kg/day group ($p<0.05$) in this test. An increase in reference errors and total error were also noted in the exposed rats compared to the controls ($p = 0.01$) and a shift in goal-oriented behavior was observed, with manganese-exposed rats exhibiting a stereotypic response strategy on a significantly greater number of session days compared to controls ($p = 0.01$). Altered expression of the dopamine D1 and D2 receptors and DAT proteins in the brain were observed in exposed rats compared to controls.

Khan, K., Factor-Litvak, P., Wasserman, G.A. et al. 2011. Manganese exposure from drinking water and children's behavior in Bangladesh. Environmental Health Perspectives. 119(10): 1501 – 1506.

Khan et al. (2011) examined the association between manganese exposure in drinking water and behavior of 8 to 11 year old children in Bangladesh. The interaction between manganese and arsenic was also examined. A total of 201 children were studied with household wells being divided into four groups: a) high arsenic (>10 µg/L) and high manganese (>400 µg/L), b) high arsenic, low manganese, c) low arsenic, high manganese, and d) low arsenic, low manganese. Children's blood and urine were analyzed for manganese, arsenic, and lead. Teachers rated children on the Tutorial Request Form (TRF) (Achenbach and Rescorla 2001, Achenbach System of Empirically Based Assessment (ASEBA), 2010), a standardized form by which teachers rate a range of child behaviors, problems, and competencies.

Significant associations were observed between water manganese levels and behavior scores. Behavior scores were divided into externalizing subscales for aggressive behavior and attention problems and internalizing subscales for withdrawal, depression, and anxiety. Water manganese levels were significantly associated with both externalizing and total TRF scores (estimated β = 2.04 and 2.59, 95th CI = 0.26 - 3.81 and 0.14 – 5.02, p=0.02 and 0.04, respectively) but were nonsignificantly associated with internalizing scores (estimated β =0.60, 95th CI = -0.11 – 1.32, p=0.10). However, after adjusting for sex, body mass index, maternal education, and arm circumference, this association also showed significance (estimated β =0.82, 95th CI = 0.08 – 1.56, p=0.03). In the final adjusted models, the associations between water manganese levels and externalizing and total TRF scores were stronger (estimated β = 2.59 and 3.35, 95th CI = 0.81 – 4.37 and 0.86 – 5.83, p=0.004 and 0.008, respectively). A dose-response relationship was observed between increased manganese levels in water and externalizing behavior problems. No statistical interaction between arsenic and manganese in water was noted.

Khan, K., Wasserman, G.A., Liu, X. et al. 2012. Manganese exposure from drinking water and children's academic achievement. Neurotoxicology. 33: 91-97.

Khan et al. (2012) studied 840 school-aged (8-11 years old) children in Bangladesh to investigate an association between manganese in water and academic achievement in mathematics and languages. Mean and median manganese concentrations in water were 1387.9 and 1301.6 µg/L, respectively , with a range of 10.0 -5710.1 µg/L. Mean and median arsenic concentrations in water were 119.5 and 81.9 µg/L, respectively, with a range of 0.1 – 1263.2 µg/L. Five categories for water manganese levels were used in the analysis, as follows: 1) ≤ 400 µg/L; 2) 401-1000 µg/L; 3) 1001 – 1440 µg/L; 4) 1441-2000 µg/L; 5) 2001 – 6000 µg/L. (400 µg/L was used as the cut-off of the lowest level of manganese as this is the WHO guideline level for manganese in water). Academic achievement was based on annual scores from the academic records of the schools for learning in Bangla, for English as a second language, and mathematics.

Children in the four highest manganese water groups showed significantly lower math test scores when compared with children in the lowest manganese group ($p = 0.03 – 0.10$). Water manganese concentrations of over 400 µg/L were associated with a 6% loss of mathematics score (CI: -12.17 to -0.47). Water arsenic was not significantly related to mathematics achievement scores ($p < 0.05$). Water manganese levels >400 µg/L were associated with 1% and 3% reductions in Bangla and English mean test scores, respectively, but the losses were not statistically significant ($p > 0.24$). Water arsenic was not related to language scores. An analysis of the comparative points lost in mathematics and language achievement due to water manganese showed that the point loss in mathematics test scores due to high levels of manganese was greater than the loss in either language test ($p < 0.01$) and this difference was statistically significant.

Ljung, K. and Vahter, M. 2007. Time to re-evaluate the guideline value for manganese in drinking water? 115 (11):1533-1538.

Ljung and Vahter (2007) examined the basis for the current WHO health-based guideline for manganese in water and its ability to protect against adverse effects in all segments of the population. The WHO guideline for manganese in water is 400 µg/L based on a NOAEL for manganese in food of 11 mg/day. To allow for a higher bioavailability of manganese in water compared to food, the NOAEL of 11 mg/day was divided by an uncertainty factor of 3. Using an adult body weight of 60 kg, a tolerable daily intake of 60 µg/kg was derived. Assuming that 20% of the total daily intake is from drinking water and that an adult consumes 2 liters of water per day, a guideline of 400 µg/L was derived. The NOAEL of 11 mg/day was based on a review by Greger (1999) that identified 11 mg/day as the upper range of manganese intake in typical Western and Vegetarian diets without adverse health effects. The Greger (1999) review cited a study where 100 Canadian women were asked to complete dietary protocols of all consumed food and beverages in their homes for 3 consecutive weekdays. The calculated daily manganese intake ranged from 0.7 to 10.8 mg/day, where 90% of the women ingested <5 mg/day, and almost half of the women ingested <2.5 mg/day. The average daily manganese intake was calculated at 3.1 ± 1.5 mg.

Manganese retention in the body is higher in infants than in adults. An increase of 3- to 4-fold manganese blood levels was detected in 1 month old infants compared with adults and decreasing manganese concentrations in hair with increasing age of children has been reported. The authors stated that this decrease in manganese concentration in hair with age is probably due to both higher absorption and lower excretion of manganese in early childhood. Although manganese is an essential element that is needed by infants to support normal brain growth and development, excessive manganese has been linked to neurobehavioral effects in children. Infant formula is one source of manganese exposure, with one study showing that standard formula contains an average of 330 µg/L manganese. The Scientific Committee on Food recommended a maximum value for manganese in infant formula of 100 µg/100 kcal, which was

below an estimated LOAEL in adults for manganese in water of 4.2 mg/L. This LOAEL was based on a study that found Parkinson-like symptoms in people older than 50 years who consumed water with a manganese concentration of 1,800 – 2,300 µg/L for longer than 10 years.

In summary, the authors stated that the manganese guideline needs to be reevaluated based on a number of questionable assumptions used in its derivation and the increasing number of reports showing infant neurotoxicity from manganese exposure.

Ljung, K.S., Kippler, M.J., Goessler, W., et al. 2009. Maternal and early life exposure to manganese in rural Bangladesh. Environmental Science and Technology. 43: 2595-2601.

Ljung et al. (2009) evaluated the associations between maternal manganese concentration in urine, blood and breast milk during early pregnancy and lactation with manganese concentration in drinking water in Bangladesh. A total of 408 pregnant women were studied, with their blood, urine, and breast milk analyzed for manganese. Water samples were analyzed for manganese and arsenic.

The mean and median manganese concentrations in the water samples were 720 µg/L and 228 µg/L, respectively, with a range of 10 to >6000 µg/L. Sixty one percent of the water samples were below the WHO guideline value for manganese of 400 µg/L and 25% were above 1,000 µg/L. Fifteen percent of the 265 water samples had concentrations of both manganese and arsenic below the guideline values (the WHO guideline value for arsenic is 50 µg/L) and 8% of the sampled wells had concentrations of both manganese and arsenic that exceeded their respective guideline values. Water manganese concentrations correlated to urine concentrations ($r_s = 0.19$, $p<0.001$), but not to blood or breast milk concentrations. No correlations were found between manganese concentrations in urine, blood, or breast milk. The median breast milk manganese concentration was 6.6 µg/kg, with a range of 2-60 µg/g. The authors concluded that the lack of association of the blood and breast milk values with the drinking water manganese concentrations was likely due to variable exposure via water and food, differences in bioavailability, and complex regulation of intestinal manganese absorption which is influenced by nutritional, physiological and genetic factors.

Menezes-Filho, J.A., Bouchard, M., de N. Sarcinelli, P. et al. 2009. Manganese exposure and the neuropsychological effect on children and adolescents: a review. Pan Am J Pub Health 26(6): 541-547.

Menezes-Filho et al. (2009) is a review article that summarized previous studies on the neuropsychological effects of manganese in children. Twelve studies were identified which were published between 1977 and 2007. Eleven of these studies reported indications of neurological effects in children from exposure to manganese in water. Two of these studies were from China where the exposed group consisted of 92 children from a town where the concentration of manganese in drinking water was between 0.24 and 0.35 mg/L, compared with

children in another town who drank water with manganese at levels <0.03 mg/L. Children from the exposed town had higher manganese levels in hair than the controls and had lower performance ($p<0.01$) than controls on 5 of 12 neurobehavioral tests. A case-control study in Canada conducted on learning disabled children found that 3rd and 4th graders with learning disabilities had significantly higher concentrations of manganese in hair, and six other elements (sodium, cadmium, copper, lead, chromium, and lithium) compared to children without learning disabilities. A study in Bangladesh investigated 54 children who drank water from wells with high manganese levels and found that increasing manganese water levels was associated with lower IQ scores on the verbal, performance, and full score scales. Another study examined the interaction of manganese and arsenic on cognitive effects in children. The results showed that high levels of both manganese and arsenic in hair were significantly associated with lower intellectual function. A Canadian study examined 46 children who were served by two wells with different manganese concentrations (0.61 mg/L vs. 0.16 mg/L). The children who drank water from the well with the higher manganese concentration had significantly higher manganese levels in hair which was associated with higher scores for hyperactive and oppositional behavior in the classroom.

Three studies reported possible adverse neurological effects from *in utero* exposure to manganese. A prospective epidemiological study on 247 women measured manganese levels in mother's hair and blood at delivery, in umbilical cord blood, and in placental tissue. A significant negative correlation was reported between manganese levels in cord blood and nonverbal scales and boys' manual ability at 3 years old. However, no relationship was found between manganese exposure and developmental scores at the 6-year follow-up. In a U.S. study, manganese in enamel of shedding teeth was used as the biomarker for manganese exposure. The children were tested for behavioral effects at 36 and 54 months, with the results showing that children with higher levels of manganese in teeth had high scores on all scales of disinhibitory behavior. A study investigated manganese concentrations in infant formula and found that hair manganese levels increased significantly from 0.19 µg/g at birth to 0.69 µg/g at 4 months in the infants fed formula, while no significant increase was observed in children who were breast fed. In addition, children with hyperactivity had significantly higher levels of manganese in hair (0.43 µg/g) than children without hyperactivity (0.27 µg/g).

Two studies examined children's exposure to manganese resulting from environmental contamination. One of these was a Spanish study that examined 100 adolescents who lived in an area of industrial contamination. Hair was analyzed for manganese, cadmium, chromium, mercury, lead, nickel and tin and no significant correlations were found between manganese levels and cognitive deficits. In contrast, a U.S. study examined children living near a mining waste site and reported that high levels of both manganese and arsenic in hair were significantly associated with lower intellectual function and verbal memory scores. A study on a case of suspected manganese intoxication in a 10-year old child who drank water from a well with very high manganese concentrations (1.21 mg/L) reported that the child did not exhibit any tremors

and had normal gait and muscle tone, but had poor verbal and visual memory as well as a decreased ability to coordinate alternating movements.

The authors concluded that most studies indicate an association between prenatal and infant exposure to manganese in drinking water and cognitive effects, however there are numerous limitations to these studies: most were cross-sectional, had a modest sample size, and lacked adjustment for important confounders. Future studies need to be conducted using larger sample sizes and more detailed exposure assessments.

Moreno, J.A., Yeomans, E.C., Streifel, K.M. et al. 2009. Aged-Dependent Susceptibility to Manganese-Induced Neurological Dysfunction. Toxicological Sciences 112(2): 394-404.

Moreno et al. (2009) investigated manganese neurotoxicity in mice exposed as juveniles, adults, or juveniles and again as adults. Male and female C57B1/6 mice were exposed to 10 or 30 mg/kg/day manganese chloride by intragastric gavage as follows: juvenile exposure, day 20-34 postnatal; adult exposure, from weeks 12 to 20; juvenile and adult exposure, day 20-34 postnatal and weeks 12-20. Manganese accumulation in brain tissue, levels of striatal catecholamines and monoamine neurotransmitter levels, and neurobehavioral parameters (locomotor changes) were examined in the treated mice.

In the juvenile mice, there was a statistically significant increase in manganese accumulation in the striatum and substantia nigra at doses of both 10 and 30 mg/kg/day. There was also a statistically significant increase in cortical manganese levels in the 30 mg/kg group. Mice exposed only as adults had a statistically significant increase in manganese in the striatum at 10 mg/kg/day and a trend toward an increase at 30 mg/kg in both the striatum and substantia nigra.

A statistically significant increase in striatal dopamine levels were noted in juvenile mice exposed to 30 mg/kg/day manganese compared to the controls and the 10 mg/kg/day groups. In mice exposed only as adults, dopamine was statistically significantly decreased in the 30 mg/kg/day group; however it was statistically significantly decreased in both the 10 and 30 mg/kg/day dose groups for mice exposed as juveniles and as adults. The dopamine metabolite, 2-(3,4-dihydroxyphenyl)acetic acid (DOPAC) was decreased in all the groups at 30 mg/kg/day ($p<0.05$), but in adults that were also exposed as juveniles, DOPAC levels were also decreased at 10 mg/kg/day ($p<0.05$).

Locomotor changes in the mice were based on open-field activity tests. Time spent in the margin was statistically significantly decreased in juvenile males at doses of both 10 and 30 mg/kg/day, but not in juvenile females. Mice exposed only as adults showed no changes in margin time, but male mice exposed to both 10 and 30 mg/kg/day as juveniles and again as adults showed a statistically significantly increased time spent in the margin. No changes in margin time were observed in female mice in any exposure group. No changes were seen in total

movements in female mice exposed as both as adults and juveniles. However, total movements were increased in male mice exposed to 30 mg/kg/day as juveniles compared with controls. No changes were observed in the total number of movements in mice exposed only as juveniles or only as adults at either dose. No significant changes were seen in total distance travelled or rearing movement in any groups.

In summary, adult mice pre-exposed to manganese as juveniles were more sensitive to manganese- induced changes in locomotor behavior and neurochemical changes in the brain than those exposed only as adults. Sex differences were also observed, with only males exhibiting neurobehavioral changes.

Parvez, F., Wasserman, G., Factor-Litvak, P. et al. 2011. Arsenic exposure and motor function among children in Bangladesh. Environmental Health Perspectives. 119(1): 1665-1670.

Parvez et al. (2011) examined whether manganese and arsenic in drinking water were associated with impaired motor function in children in Bangladesh. A total of 304 children (8 -11 years of age) were studied, with samples of their drinking water, urine, blood, and toenails analyzed for arsenic and manganese. Maternal intelligence was measured on the Wechsler Abbreviated Scale of Intelligence and motor function was measured in children using the Bruininks-Oseretsky test[2].

The mean water manganese concentration across all water samples was 725.5 µg/L and the mean arsenic concentration across all water samples was 43.3 µg/L. Water levels of manganese and arsenic were used to divide the data into four exposure groups: 1) low arsenic levels (mean of 2.3 µg/L) and low manganese (mean of 202.1 µg/L); 2) low arsenic (mean of 3.3 µg/L) and high manganese (mean of 1111.1 µg/L); 3) high arsenic (mean of 97.3 µg/L) and low manganese (mean of 184 µg/L); and 4) high arsenic (mean of 70.7 µg/L) and high manganese (mean of 1367.1 µg/L) for the purpose of evaluating the association between water levels and motor function. Blood manganese had a mean concentration of 14.7 µg/L.

No significant associations were observed between manganese exposure and motor function. Children exposed to higher water manganese levels (> 500 µg/L) did not have higher levels of blood manganese (14.5 vs. 15.0 µg/L, $p = 0.17$) but did have higher levels of nail manganese (27.0 vs. 33.8 µg/g, $p < 0.05$). Blood manganese correlated positively with blood arsenic and arsenic exposure was associated with decreased motor function. It was concluded that arsenic exposure was adversely associated motor function.

[2] The Bruininks-Oseretsky test measures a wide range of motor skills that generates scores based on the coordination of arms and hands, posture and balance, and locomotion.

Riojas-Rodriguez, H., Solis-Vivanco, R., Schilmann, A. 2010. Intellectual function in Mexico children living in a mining area and environmentally exposed to manganese. Environmental Health Perspectives. 118(10: 1465-1470.

Riojas-Rodriguez et al. (2010) examined the exposure to airborne manganese from mining and processing and its association with intellectual function in children 7 to 11 years old. Seventy nine children from communities in a mining area and 93 children from nonexposed communities were studied. Manganese was analyzed in blood and hair and the children were tested for intellectual function using the revised version of the Wechsler Intelligence Scale for Children.

The 24-hour median manganese level in PM_{10} in the exposed communities was 0.13 $\mu g/m^3$ compared to a median level of 0.02 $\mu g/m^3$ in the control communities. Manganese concentrations in blood and hair showed a weak but significant correlation ($r = 0.22$, $p < 0.01$). The median concentration of manganese in hair was almost 20 times higher in the exposed group (12.6 µg/g) than in the control group (0.6 µg/g). No significant sex differences were observed for manganese in blood or in hair.

Manganese in hair was significantly inversely associated with verbal IQ ($\beta = -0.29$; 95% CI = -0.51 to -0.81); performance IQ ($\beta = -0.08$; 95% CI = -0.32 to 0.16); and total scale IQ ($\beta = -0.20$; 95% CI = -0.42 to -0.02) as determined by a simple regression model. Manganese in blood was nonsignificantly inversely associated with total and verbal IQ.

Roels, H.A., Bowler, R.M., Kim, Y., et al. 2012. Manganese exposure and cognitive deficits: A growing concern for manganese neurotoxicity. Neurotoxicology. 33: 872-880.

Roels et al. (2012) is a review article that covers presentation at a symposium dealing with recent findings on manganese-related cognitive and motor changes from both occupational and environmental epidemiological studies. The occupational data are not relevant to CCL. Thus, this summary applies only to the environmental data and the oral exposure route.

A study on the neurodevelopmental effects among children exposed to manganese at a very young age reported a U-shaped association between 12-month blood manganese levels and mental development. These results suggest that both low and high blood manganese levels may have adverse neurological effects. Four studies examined exposure to manganese in drinking water and its association on cognitive performance. One of these studies was in China, two in Bangladesh, and one in Canada and they all showed an inverse relationship between manganese in water and/or biomarkers of manganese exposure and cognitive performance. Combining the results from the studies in Mexico, Brazil, and Canada showed a decrease in Full IQ of 2.62 points for a 10-fold increase in hair manganese, with a greater loss estimate in girls compared to boys (-4.19, 95% CI -6.19 to -2.07) and (-1.08, 95% CI -3.21 to -1.05) (p=0.04).

Santamaria, A.B. and Sulsky, S.I. 2012. Risk assessment of an essential element: manganese. Journal of Toxicology and Environmental Health. Part A: 128-155.

Santamaria and Sulsky (2012) is a review of the essentiality and toxicity of manganese.

Essentiality:

Manganese is an essential element and is required for growth, development, and maintenance of health. The element is required for skeletal system development, energy metabolism, enzyme activation, nervous system functioning, and functioning of reproductive hormones, and is an antioxidant that protects cells from free radical damage. Manganese is naturally occurring in food, with the highest concentrations usually found in nuts, cereals, legumes, fruits, vegetables, grain, and tea. Typical daily intakes range from 2 to 9 mg/day for adults, and 3-5% is absorbed from the gastrointestinal tract. Mineral and vitamin supplements may contain 1 to 20 mg/tablet. The Institute of Medicine established an adequate intake (AI) of manganese for adults of 1.8 – 2.3 mg/day and an upper limit (UL) of 11 mg/day. The AI and UL for infants, children, and adolescents are as follows: 0-6 months: AI = 0.003 mg/day, UL – not established; 7-12 months: AI = 0.6 mg/day, UL not established; 1-3 yrs: AI = 1.2 mg/day, UL = 2 mg/day; 4-8 yrs: AI = 1.5 mg/day, UL = 3 mg/day; 9-13 yrs: AI = 1.6 – 1.9 mg/day, UL = 6 mg/day; 14-18 yrs: AI = 1.6-2.2 mg/day, UL = 9 mg/day.

Toxicity:

In experimental animals, toxicity from manganese is not usually observed until concentrations are greater than 1 mg/g diet. In humans, a few studies have reported adverse neurological effects following ingestion of high levels of manganese or following chronic exposure to manganese in drinking water. In one cross-sectional study, the concentration of manganese was estimated to be at least 28 mg/L in the water with adverse health effects including lethargy, tremor, and mental disturbances reported. Several studies have demonstrated a negative association between manganese in water and cognitive function, as measured by verbal, performance, and full-scale IQ tests.

Manganese neurotoxicity through occupational exposure has been most commonly associated with occupations such as manganese mining and smelting, battery manufacturing, and steel production. In occupational studies, neurotoxicity, consisting primarily of effects on motor function and cognitive function, has mainly been observed when workers were chronically exposed to levels of manganese >1 mg/m^3. A review of 18 occupational studies published between 1986 and 2007 concluded that the literature on occupational exposure to manganese is "consistent with the existence of an early, dose-dependent neurological effect of low-level manganese exposure." This review also concluded that "not all the studies showed coherent results, even while using the same and most sensitive tests."

Current regulations and guidelines for manganese for inhalation exposure are mainly based on the same occupational study (Roels et al., 1992). However, different values were derived based on using different NOAELs, LOAELs, or benchmark dose levels and uncertainty factors, with uncertainty factors ranging from 50 to 1000. The EPA RfD is 0.14 mg/kg/day, the EPA SMCL (based on the aesthetic properties of manganese) is 0.05 mg/L in water and the WHO drinking water guideline (health-based) is 0.4 mg/L. In the future, PBPK modeling may be used to improve the risk assessments of manganese, by providing data on the movement of manganese throughout the body and determining the relative contribution of inhaled and ingested manganese to tissue levels in target organs.

Santamaria, A.B. 2008. Manganese exposure, essentiality, and toxicity. Indian J Med Res. 128: 484-500.

Santamaria (2008) is a review of the exposure, essentiality, and toxicity of manganese. Manganese plays an essential role in regulation of cellular energy, bone and connective tissue growth, and blood clotting. It has three primary metabolic functions: 1) as an activator of the gluconeogenic enzymes pyruvate carboxylase and isocitrate dehydrogenase, 2) protecting mitochondrial membranes through superoxide dismutase, and 3) activation of glycosyl transferase, an enzyme involved in mucopolysaccharide synthesis. Only a few cases of manganese deficiency have been reported in humans, with symptoms including dermatitis, slowed growth of hair and nails, decreased serum cholesterol levels and decreased levels of clotting proteins. Dietary studies have demonstrated that dietary intake of manganese at levels of 0.8 to 20 mg for 8 weeks do not result in adverse health effects in healthy adults.

The first report of the neurological effects of manganese was in 1837, in which five men working in a manganese ore crushing plant in France were reported to have muscle weakness, whispering speech, salivation, and bent posture. These symptoms were later termed “manganism”: a neurodegenerative disease characterized by central nervous system abnormalities and neuropsychiatric disturbances. Manganism resembles Parkinson’s disease, but there is evidence that different parts of the brain are affected; Parkinson’s disease is associated with the loss of dopaminergic neurons within the substantial nigra and manganism is associated with hyperintense signal abnormalities in the globos pallidus, striatum, and substantial nigra. Manganese neurotoxicity has been most commonly associated with occupations such as manganese mining and smelting, battery manufacturing, and steel production.

Blood and urine manganese are the most commonly used biomarkers of exposure in occupational studies. Normal whole blood levels of manganese range from 7-12 µg/L and serum levels range from 0.6 - 4.3 µg/L. Hair may not be the best indicator of occupational exposure, as external manganese exposures may affect the levels in hair, limiting its usefulness as a biomarker of internal dose. In most studies, manganese in blood has been used as an indicator of exposure over the previous month and manganese in urine to indicate exposure over the previous few days.

There are difficulties in measuring past exposures because excess manganese is usually removed from the body within a few days after cessation of the exposure.

Studies on the association between manganese exposure in workers, as measured by blood or urine levels, and neurological measures have shown mixed results. Some studies have reported an association, usually on the group level rather than on the individual level, while others have shown no association. A variety of studies have attempted to determine the threshold exposure level for manganese neurotoxicity. The study that was used as the basis for the EPA RfC for manganese (Roels et al., 1992) reported increased neurobehavioral deficits in workers exposed to mean respirable levels of 0.215 mg/m^3 manganese. EPA derived a LOAEL of 0.15 mg/m^3 by dividing 0.215 mg/m^3 by years of exposure. Benchmark dose modeling of the Roels et al. study and two other studies derived a $BMDL_{10}$ ranging from 0.10 – 0.27 mg/m^3. These results suggest that at these manganese exposure levels, there is little risk of workers developing neurobehavioral effects.

Conducting risk assessments on essential trace elements such as manganese is challenging because of the need to consider both essentiality and toxicity. Two ranges of intake need to be considered: intakes that are too low and can lead to nutritional deficits and those that are too high and can lead to toxic effects. Defining these ranges quantitatively is challenging and other issues, such as homeostatic regulation in the body, need to be considered as well.

Yoon, M., Nong, A., Clewell, H. et al. 2009a. Lactational transfer of manganese in pups: predicting manganese tissue concentration in the dam and pups from inhalation exposure with a pharmacokinetic model. Toxicological Sciences. 112(1): 23-43.

Yoon et al. (2009a) modified a previous manganese PBPK model developed for adult rats (Nong et al., 2009) to include the lactating dam and neonates. The model was based on rats exposed to manganese through the diet alone or through the diet and inhalation exposure. The model used as many parameters from the adult rat model as possible and changed a number of parameters for the neonatal rat and lactating dam. A "virtual" milk compartment was added to the model, this compartment carried a mass of manganese from the dam to the pup, with a variable production rate for milk over the lactation period. Daily manganese dose to the pups included three sources: milk, diet, and inhalation. Some pharmacokinetic parameters in young pups were different from those in the adults, including a lower basal level of biliary excretion of manganese, higher intestinal absorption and retention during the early postnatal period, and different tissue-binding capacities.

The PBPK model was used to predict manganese concentrations observed in various experiments in rats. Concentrations of manganese in the dam after cessation of exposure on PND 18 were predicted using the model for various manganese concentration levels and compared with the results from experimental data. In addition, the model-predicted tissue concentrations were

compared with the experimental data for both the dams and the pups. The model-predicted manganese concentrations in the striatum or liver in the pups during the postnatal period and the model-predicted manganese dose from milk were also compared with the experimental data.

The results showed that the simulated maternal and neonatal tissue manganese concentrations were in reasonable agreement with the experimental data. Simulated milk manganese concentrations were consistent with the observed values both for normal lactation and conditions of inhalation exposure. The neonatal concentrations of manganese in both the striatum and liver were consistent with the experimentally-determined values. However there were inconsistencies between modeled and observed values for the blood and lung. A comparison of manganese levels in the striatum between the dams and pups showed that the levels in the striatum were similar between the two, and did not differ substantially from the non-lactating adult.

Yoon, M., Nong, A., Clewell, H. et al. 2009b. Evaluating placental transfer and tissue concentrations of manganese in the pregnant rat and fetuses after inhalation exposures with a PBPK model. Toxicological Sciences. 112(1): 44-58.

Yoon et al. (2009b) developed a manganese gestational PBPK model based on a previous manganese model for the adult rat (Nong et al., 2009). The goal of the model was to predict manganese fetal doses and manganese disposition in the dam and fetus in rats following maternal inhalation exposure to manganese. Similar to the model described in Yoon et al. (2009a), the model used as many parameters as possible from the adult model but changed a number of parameters for the pregnant dam and fetus.

The model predicted maternal and fetal tissue concentrations on GD20, immediately after the cessation of the last inhalation exposure, for each manganese inhalation concentration. The predicted concentrations were compared to experimental data for tissues and brain manganese levels. The manganese daily dose to the fetus on GD20 was determined based on the difference between the amount of manganese transferred to the fetus from GD0 to GD20 and from GD0 to GD21.

The simulated manganese concentrations in the placenta and in the brain on GD20 at the end of the last exposure were consistent with that observed in the experimental data. A comparison of the internal exposures between the mother and fetus, 24 hour manganese concentrations for whole brain (fetus) or cerebellum (dam) or blood on GD 20 were compared. The exposure level in the fetal brain was lower than in equivalent tissues in the dam at all concentrations. Blood levels also showed that the internal exposures in the fetus were lower or comparable to those in the dam. The authors concluded that "these simulations support the finding that manganese inhalation during gestation up to 1 mg/m^3 did not increase fetal manganese exposure in the brain and consequently there was no noticeable dose-dependent increase in manganese exposure at the target tissue in the fetus."

Yoon, M., Schroeter, J.D., A. Nong, et al. 2011. Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: describing manganese homeostatis during development. Toxicological Sciences 122(2): 297-316.

Yoon et al. (2011) developed a series of PBPK models for describing manganese kinetics during fetal and neonatal development in humans. These models were based on the PBPK rat models developed in Yoon et al. (2009a,b) which: 1) described placental manganese transfer by active transport while maintaining homeostasis of manganese; 2) described transfer of manganese from maternal milk to the neonate using a diffusion-mediated secretion; 3) described higher absorption of manganese in neonates while nursing, 4) considered biliary excretion to be at a low level but inducible in neonates, 5) considered different neonatal and adult gastrointestinal absorption and biliary excretion rates, 6) allowed for increased brain uptake of manganese during fetal development and in neonates. Species differences between rats and humans were also taken into account based on comparative physiology and on age-dependent changes in the pharmacokinetics of manganese.

The model simulated placental transfer of manganese for different inhalation exposure concentrations: 0, 0.001, and 0.01 mg/m^3. Placental manganese concentrations did not change following exposure to 0.001 mg/m^3 but increased by 18% at 0.01 mg/m^3; however, this increase was still within the range of normal variation. An 11% increase in fetal globus pallidus manganese was seen in the simulated 0.01 mg/m^3 concentration; this increase was also within the range of normal variation. The model suggests that no appreciable accumulation of manganese in the fetus is expected after typical environmental exposures to manganese in the mother.

The simulated change in manganese concentration in maternal milk after exposure to 0.01 mg/m^3 manganese was less than 10% compared to the change in the diet-only exposure. The model simulated that manganese concentration in the globus pallidus in the neonate was similar to that in the adults, however during nursing it was lower than in the adults. Two additional concentrations of manganese (0.1 mg/m^3 and 0.5 mg/m^3) were simulated in the model to examine whether fetal or neonatal brain manganese changes after exposure to high concentrations of manganese are different from those in adults. The neonatal brain appears to show a similar dose-response pattern as seen in adults, with manganese accumulation starting at about 0.01 mg/m^3 in nursing infants and in children. These results suggest that no appreciable brain accumulation of manganese would be expected in neonates after typical environmental exposure conditions.

A comparison of the manganese doses after placental transfer, milk, diet, or inhalation exposure were compared for the fetus, nursing infants, and adults. The model predicted that there would be no significant increases in placental dose to the fetus after maternal exposure to $\leq$ 0.01 mg/m^3. The model was evaluated using reported human blood and tissue manganese concentrations, with good correspondence between the model-predicted and reported concentrations.